Intravitreal Dexamethasone Implant as an Adjunct Weapon for Severe and Refractory Uveitis in Behçet's Disease

Claudia Fabiani MD PhD[1], Giacomo Emmi MD PhD[2], Giuseppe Lopalco MD[4], Lorenzo Vannozzi MD PhD[3], Daniela Bacherini MD[3], Silvana Guerriero MD PhD[5], Rossella Franceschini MD[6], Bruno Frediani MD[7], Florenzo Iannone MD PhD[4], Gian Marco Tosi MD[6], Donato Rigante MD[8]* and Luca Cantarini MD[7]*

[1]Department of Ophthalmology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy
[2]Department of Experimental and Clinical Medicine and [3]Department of Surgery and Translational Medicine, Eye Clinic, University of Florence, Florence, Italy
[4]Department of Emergency and Organ Transplantation, Rheumatology Unit and [5]Department of Ophthalmology and Otolaryngology, University of Bari, Bari, Italy
[6]Ophthalmology and Neurosurgery Department and [7]Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy
[8]Institute of Pediatrics, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica Sacro Cuore, Rome, Italy

ABSTRACT: **Background:** The evidence on the use of dexamethasone implants in the treatment of Behçet's disease (BD)-related uveitis is limited to a few cases.

Objectives: To evaluate the efficacy of dexamethasone implants on ocular functional, morphological, and clinical parameters in BD patients with severe refractory uveitis.

Methods: Five eyes from five BD patients were enrolled. A single intravitreal dexamethasone injection was applied to each eye. Best corrected visual acuity (BCVA), central macular thickness (CMT) assessed with optical coherence tomography, retinal vasculitis assessed by fluorescein angiography, vitreous haze score (Nussenblatt scale), intraocular pressure (IOP), and lens status (LOCS III, Lens Opacities Classification System III) were recorded at baseline and at 1, 3, and 6 month follow-up visits.

Results: At baseline, all eyes showed marked macular edema and 4/5 had concomitant active retinal vasculitis. Mean BCVA was increased from baseline at each control visit with a mean improvement of 0.26 ± 0.18 lines at 6 months follow-up. Mean CMT decreased from baseline at each control visit with a mean improvement at 6 months follow-up of 198.80 ± 80.08 µm. At the end of the study, none of the eyes showed macular edema and the mean CMT was 276.80 ± 24.94 µm. Retinal vasculitis resolved in all eyes. One eye experienced an IOP spike during treatment that resolved spontaneously, and one eye developed a clinically significant lens opacity at 6 months follow-up.

Conclusions: Treatment with a dexamethasone implant in BD-uveitis and inflammatory macular edema was safe and effective as an additional treatment combined with systemic immunomodulatory drugs.

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KEY WORDS: uveitis, macular edema, Behçet's disease, intravitreal treatment, dexamethasone implant

*The last two authors contributed equally to this study

Bipolar aphthosis and severe intraocular inflammation leading to sight-threatening sequelae are the main features of Behçet's disease (BD) [1]. BD-related posterior uveitis and panuveitis are the most significant causes of morbidity ranging from 50 to 70% of cases, and blindness is reported with a frequency rate of about 25% [2]. According to the European League against Rheumatism (EULAR) recommendations, any patient with BD-related inflammatory eye disease affecting the posterior segment should be treated with azathioprine and systemic glucocorticoids [3]. In case of severe eye disease, defined as > 2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease (retinal vasculitis or macular involvement), it is recommended that either cyclosporine A or infliximab be used in combination with azathioprine and glucocorticoids. Alternatively interferon-alpha with or without glucocorticoids might be used instead [3].

Over the past years, increasing evidence has shown that the intravitreal delivery of glucocorticoids may be useful to induce the remission of intraocular inflammation in refractory BD-related ocular involvement or in the most severe cases. A few studies have explored the efficacy and safety of intravitreal injection of triamcinolone acetonide and fluocinolone acetonide implant in BD (Retisert®, Bausch & Lomb, Rochester, NY, USA) [4]. Most authors have also suggested the need to closely monitor intraocular pressure (IOP) and lens clarity since a consistent percentage of treated eyes may develop glaucoma and/or cataract. However, the bio-erodible intravitreal dexamethasone implant, now licensed for the treatment of adult and pediatric noninfectious intermediate and posterior uveitis in the United States and Europe, has shown a better safety profile compared to other drugs. Moreover the clinical efficacy of a dexamethasone implant in the treatment of non-infectious posterior uveitis has been assessed in several randomized controlled clinical trials [5-7]. Nevertheless, with regard to BD-related uveitis, the

evidence on the use of a dexamethasone implant is limited to a few cases [8].

In the present study we aimed at evaluating the efficacy of a dexamethasone implant on ocular functional, morphological, and clinical parameters in a small case series of BD patients with severe refractory and/or long-standing uveitis.

PATIENTS AND METHODS

We performed a retrospective review of the medical records of patients treated with a dexamethasone implant (Ozurdex®; Allergan, Inc, Irvine, CA, USA) for persistent macular edema secondary to BD-related uveitis in three uveitis referral centers in Italy (Universities of Siena, Florence, and Bari). Diagnosis of BD was based on the International Study Group Criteria (ISGC) [9] and/or International Criteria for BD (ICBD) [10]. Patients were considered to have persistent inflammatory macular edema if they had central macular thickness (CMT) greater than 300 microns and fluid in the macula (cysts or subretinal fluid), as assessed with optical coherence tomography (OCT) and fluorescein angiography (FA), for longer than 3 months before a dexamethasone implant treatment.

Demographic and clinical characteristics of patients are shown in the Table 1. The following ophthalmic clinical parameters were recorded at all-time points (baseline, 1 month, 3 month, 6 month follow-up): best corrected visual acuity (BCVA), CMT measured by OCT, presence of macular edema and retinal vasculitis assessed with FA, vitreous haze (VH) grading according to Nussenblatt scale, and IOP values [11]. Lens status and cataract grading according to LOCS III classification system was recorded at baseline and at 6 months [12].

Only patients who had been followed for at least 6 months were included in the study. The implant was injected by a standard procedure under topical anesthesia. After the injection, a topical antibiotic was applied 4 times a day for 7 days. All patients gave written informed consent for the dexamethasone implantation. Data were statistically described by mean values and standard deviation for continuous variables and by ranges for discrete variables.

RESULTS

Five eyes of five BD patients were included in the study. All patients fulfilled both the ISGC and ICBD diagnostic criteria for BD. Three patients were male and two patients were female, with age ranging from 38 to 52 years. Four eyes were phakic and one eye was pseudophakic. At baseline OCT and FA revealed the presence of cystoid macular edema (CME) in all eyes, and 4/5 eyes showed concomitant fluorangiographic evidence of active retinal vasculitis. None of the patients had activation of uveitis in the fellow eye during the follow-up period. Table 2 shows previous and concomitant treatments with disease modifying anti-rheumatic drugs (DMARDs), biologic agents, glucocorticoids and colchicine. Only one eye (patient II) experienced

Table 1. Demographic and clinical characteristics of patients

Patient	Gender	Age (years)	Age at disease onset (years)	HLA B51 (Y/N)	Disease duration (years)	Characteristics of eye involvement	Mucosal involvement (Y/N)	Skin (Y/N)	CNS (Y/N)	SNP (Y/N)	Fever (Y/N)	Gut (Y/N)	Vascular (Y/N)	Joint (Y/N)	ISGC (Y/N)	ICBD (Y/N)
1	F	52	49	Y	3	Bilateral panuveitis	Y	Y	N	N	N	N	N	Y	Y	Y
2	M	38	18	Y	20	Panuveitis	Y	Y	Y	N	Y	N	Y	Y	Y	Y
3	M	46	42	N	4	Bilateral panuveitis	Y	Y	N	N	N	N	N	N	Y	Y
4	M	45	28	N	17	Bilateral posterior uveitis	Y	N	N	N	Y	Y	N	Y	Y	Y
5	F	43	35	Y	8	Posterior uveitis	Y	Y	N	N	Y	Y	Y	N	Y	Y

Y = yes, N = no, F = female, M = male, CNS = central nervous system, SNP = peripheral nervous system, ISGC = International Study Group Criteria, ICBD = International Criteria for Behçet's Disease

Table 2. Previous and concomitant treatments of the patients enrolled

Patient	Previous biologic agents	Previous DMARDs (Y/N)	Previous DMARDs	Previous GC (Y/N)	Previous colchicine (Y/N)	Concomitant biologic agent	Concomitant DMARD and dosage	Concomitant GC (Y/N)	Concomitant colchicine (Y/N)	DEX IVT implant (RE, LE)	Reason for performing DEX IVT implant
1	-	Y	AZA, MTX	Y	Y	N	CycA 2,5 mg/kg/die	Y	Y	RE	CME, retinal vasculitis
2	ADA	Y	AZA; MTX	Y	Y	GOL		N	Y	LE	CME, retinal vasculitis
3	ADA, CZP IFX, ANA, CAN	Y	CycA, MTX	Y	N	N	MMF 1.5 g/die	Y	N	RE	CME, retinal vasculitis
4	ADA	N		Y	N	IFX		Y	N	RE	CME
5	IFX	Y	AZA, MTX	Y	N	N	AZA 2,5 mg/kg/die	Y	N	RE	CME, retinal vasculitis

Y = yes, N = no, DMARDs = disease modifying antirheumatic drugs, GC = glucocorticoids, DEX = dexamethasone, IVT = intravitreal, RE = right eye, LE = left eye, CME = cystoid macular edema, ADA = adalimumab, CZP = certolizumab pegol, IFX = infliximab, GOL = golimumab, ANA = anakinra, CAN = canakinumab, MTX = methotrexate, AZA = azathioprine, CycA = cyclosporine A

a mild recurrence of vitreous haze at the 6 month follow-up visit, while the remaining eyes did not show the recurrence of uveitis during the entire follow-up. Table 3 illustrates the main functional and morphological parameters collected at baseline and at each follow-up visit in the affected eyes (BCVA, CMT, vasculitis and vitreous haze). Table 4 summarizes the lens status at baseline and at the end of the study, and IOP values at each time-point.

The mean BCVA, CMT, and vitreous haze score improved over the follow-up period. The mean BCVA increased from baseline (0.44 ± 0.29) at each control visit with a mean improvement at the 1 month visit of 0.06 ± 0.05, at the 3 month visit of 0.18 ± 0.10, and at the 6 month visit of 0.26 ± 0.18. The mean CMT decreased from baseline (475.60 ± 98.81) at each control visit with a mean improvement at the 1 month visit of 97.80 ± 77.77, at the 3 month visit of 193.40 ± 81.90, and at the 6 month follow-up of 198.80 ± 80.08. At the end of treatment none of the eyes showed signs of macular edema with a mean CMT of 276.80 ± 24.94. At baseline retinal vasculitis was diagnosed in 4/5 eyes, while it was not observed in all eyes at 3 and 6 month follow-up visits. One eye experienced an IOP spike (> 20 mmHg) during treatment that resolved spontaneously, and only one eye developed a clinically significant lens opacity at 6-month follow-up. No additional side effects that could be related to the dexamethasone implant injection were observed. In one eye (patient IV) vitreoretinal surgery was performed along with cataract extraction before the dexamethasone implant was given, because of the occurrence of hemovitreous.

Table 3. BCVA, CMT, vasculitis and vitreous haze at baseline and at each follow-up visit of the five BD-patients enrolled

Patient	BCVA T0 (baseline)	BCVA T1 (1-month)	BCVA T2 (3-month)	BCVA T3 (6-month)
1	0.1	0.2	0.4	0.5
2	0.8	0.8	1.0	0.9
3	0.7	0.8	0.9	0.9
4	0.3	0.3	0.5	0.8
5	0.3	0.4	0.3	0.4
Patient	**CMT T0 (baseline) (microns)**	**CMT T1 (1-month) (microns)**	**CMT T2 (3-month) (microns)**	**CMT T3 (6-month) (microns)**
1	453	254	252	260
2	560	552	278	309
3	350	298	278	267
4	590	435	340	297
5	425	350	263	251
Patient	**Vasculitis T0 (baseline) (Y/N)**	**Vasculitis (1 months) (Y/N)**	**Vasculitis (3 months) (Y/N)**	**Vasculitis (6 months) (Y/N)**
1	Y	N	N	N
2	Y	N	N	N
3	Y	N	N	N
4	N	N	N	N
5	Y	Y	N	N
Patient	**Vitreous haze T0 (baseline) (Nussenblatt scale)**	**Vitreous haze (1 month) (Nussenblatt scale)**	**Vitreous haze (3 month) (Nussenblatt scale)**	**Vitreous haze (6 month) (Nussenblatt scale)**
1	0	0	0	0
2	1+	1+	0	1+
3	3+	1+	0	0
4	Vitrectomized	Vitrectomized	Vitrectomized	Vitrectomized
5	0	0	0	0

Y = yes, N = no, BCVA = best corrected visual acuity, CMT = central macular thickness

DISCUSSION

In BD ocular involvement the cumulative structural damage and the vision loss result from recurrent episodes of inflammation [13]. The goal of treatment should not only be to suppress inflammation when it occurs, but also to prevent severe recurrent attacks of intraocular inflammation and to attain complete remission of inflammation in the longer term. In our patients, a single intravitreal injection of a dexamethasone implant was safe and effective in the treatment of BD posterior uveitis or panuveitis, refractory to systemic glucocorticoids and/or DMARDs or biologic agents. Indeed, at the 6-month follow-up, treatment with dexamethasone implant was highly effective in resolving CME and retinal vasculitis in all cases. These findings occurred in parallel with the improvement of visual function (BCVA), which was also recorded in all eyes. Our observations are consistent with the results of the pivotal clinical trials and real-world data on the use of dexamethasone implants in the treatment of non-infectious uveitis. Indeed, in most studies, a high efficacy has been observed in terms of improvement of all ocular functional and morphological parameters [5, 14-18]. Our results are also in line with a recently published retrospective multicenter study on BD refractory uveitis [8]. Coşkun et al. [8] investigated the results of a single dexamethasone implant in the treatment of 17 eyes of 12 patients with refractory Behçet posterior uveitis at 1, 3, 6, and 12 months follow-up. BCVA, CMT, vitreous haze

Table 4. The lens status at baseline and at the end of the study and the IOP at baseline and at each follow-up visit following the intravitreal dexamethasone implantation

Patient	Lens status before implant (LOCS III)	Lens status after implant (6 months) (LOCS III)	IOP T0 (baseline) (mmHg)	IOP T1 (1 month) (mmHg)	IOP T2 (3 months) (mmHg)	IOP T4 (6 months) (mmHg)
1	0	0	13	13	16	13
2	0	0	13	14	19	17
3	NCP1	NCP4	14	16	16	15
4	Pseudophakic	Pseudophakic	12	15	14	14
5	0	0	16	16	16	16

IOP = intra ocular pressure, T = time, NCP = nuclear cortical and posterior/subcapsular, LOCS III = Lens Opacities Classification System III

score, and IOP were determined, at baseline and control visits. BCVA significantly increased from baseline at each control visit and the mean CMT and vitreous haze score were significantly decreased from baseline at each follow-up visit. Three eyes showed IOP spikes requiring topical treatment. The efficacy of intravitreal delivery has been investigated in BD also for other glucocorticoids, such as triamcinolone acetonide and fluocinolone acetonide [19-25]. In 2014 Park and co-authors [19] investigated the effectiveness of intravitreal triamcinolone acetonide (4 mg/0.1 ml) injection for refractory posterior BD uveitis at 24-month follow-up. Forty-nine patients (49 eyes) were included. Mean BCVA was improved at 12 and 24 month evaluations. A complete control of intraocular inflammation was obtained in 87.0% of patients, but 60.0% of them showed a disease relapse within 12 months. IOP pressure elevation (> 21 mmHg) was observed in about 40% of cases [19]. The study results suggested that intravitreal triamcinolone acetonide is effective in severe BD eye involvement, but ocular complications are commonly observed and may limit triamcinolone acetonide efficacy and repeatability. Oh and colleagues [20] reported the long-term outcome and complications of eight eyes from seven patients with BD-related uveitis treated with a 0.59 mg fluocinolone acetonide intravitreal implant. Although the final significant visual acuity improved, the authors reported a high rate of complication in terms of postoperative IOP spikes, with up to 62% of eyes requiring glaucoma shunting surgery [20]. They also reported a case of postoperative cytomegalovirus endothelitis. Fluocinolone acetonide efficacy has been also evaluated by Sangwan et al. [21] in a prospective multicenter randomized double-masked dose-controlled study. The three-year results have shown that the fluocinolone acetonide implant significantly reduced uveitis recurrence rates and also improved visual acuity, allowing the reduction in adjunctive therapy. Fourteen BD-patients were included in the study. Elevation of IOP occurred in about 70% of patients, and nearly all (94.9%) phakic implanted eyes required cataract surgery [21].

Regarding dexamethasone implant-related ocular complications, it is notable that the good safety observed in previously published studies in non-infectious uveitis and BD-related uveitis has been replicated in our series. To confirm these encouraging findings in BD-related uveitis, properly designed ad hoc studies including larger cohorts of patients and with longer follow-up are needed. The number of injections required to control intraocular inflammation in BD-related uveitis is still controversial and the effect of repeated dexamethasone injections needs to be clarified.

CONCLUSIONS

In conclusion, our data suggest considering the intravitreal administration of a dexamethasone implant in the treatment of BD intraocular inflammation, especially when complicated by CME not adequately controlled by systemic therapy. Additional benefits are noted when ocular inflammation is unilateral or asymmetric, when local therapy may prevent the need to increase the dose of systemic administered medications. Individual patients' characteristics should guide the treatment with dexamethasone implant in the daily clinical practice.

Correspondence
Dr. C. Fabiani
Dept. of Ophthalmology, Humanitas Clinical and Research Center, Rozzano, Milan 53100, Italy
Phone: (+39) 34084-84873
Fax: (+39) 06481-9648
email: claudia.fabiani@gmail.com

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Capsule

Blockade of TANK-binding kinase 1/IKKε inhibits mutant stimulator of interferon genes (STING)-mediated inflammatory responses in human peripheral blood mononuclear cells

Gain-of-function mutations in *TMEM173*, encoding the stimulator of interferon genes (STING) protein, underlie a novel type I interferonopathy that is minimally responsive to conventional immunosuppressive therapies and associated with high frequency of childhood morbidity and mortality. STING gain-of-function causes constitutive oversecretion of interferon. Fremond et al. studied the effects of a TANK-binding kinase 1 (TBK-1)/IKKε inhibitor (BX795) on secretion and signaling of interferon in primary peripheral blood mononuclear cells (PBMCs) from patients with mutations in STING. PBMCs from four patients with STING-associated disease were treated with BX795. The effect of BX795 on interferon pathways was assessed by western blotting and an interferon β reporter assay as well as by quantification of interferon α in cell lysates, staining for STAT-1 phosphorylation, and measurement of interferon-stimulated gene (ISG) messenger RNA (mRNA) expression. Treatment of PBMCs with BX795 inhibited the phosphorylation of interferon regulatory factor 3 and interferon β promoter activity induced in HEK 293T cells by cyclic GMP-AMP or by genetic activation of STING. In vitro exposure to BX795 inhibited interferon α production in PBMCs in patients with STING-associated disease without affecting cell survival. In addition, BX795 decreased STAT-1 phosphorylation and ISG mRNA expression independent of interferon α blockade. These findings demonstrate the effect of BX795 on reducing type I interferon production and interferon signaling in cells from patients with gain-of-function mutations in STING. A combined inhibition of TBK-1 and IKKε therefore holds potential for the treatment of patients carrying STING mutations, and may also be relevant in other type I interferonopathies.

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Eitan Israeli

Capsule

Defining low disease activity in systemic lupus erythematosus

Polachek et al. set out to define and identify a group of systemic lupus erythematosus patients with low disease activity (LDA) and to examine whether LDA is similar to patients in remission and different from a high disease activity group (HDA) in short-term outcomes. The LDA group was defined as Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) < 3, including only one clinical manifestation of rash, alopecia, mucosal ulcers, pleurisy, pericarditis, fever, thrombocytopenia, or leukopenia. The patients could be taking anti-malarials. Remission was defined as no clinical manifestation from taking anti-malarials alone, and the HDA group was defined as SLEDAI-2K › 6. The time frame for inclusion in each group was at least 1 year. Of 620 patients with active disease who were seen between 1970 and 2015, 80 patients (12.9%) fulfilled the criteria for LDA, 191 (30.8%) for remission, and 349 (56.3%) for HDA. Polachek et al. found that the LDA patients with and without positive serology results were similar at baseline and with prior disease characteristics. After 2 years of follow-up, the LDA and remission groups were similar in their adjusted mean SLEDAI-2K score, organ involvement, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score, mortality, and therapies. After 2 and 4 years of follow-up, the HDA group had a higher adjusted mean SLEDAI-2K score, more major organ involvement, higher SDI score, higher mortality, and more therapy compared to the combined LDA/remission groups. LDA and remission groups had similar short-term outcomes, and both had better outcomes and prognosis than the HDA group. LDA may be used as an outcome measure in therapeutic trials or in treat-to-target regimens.

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Eitan Israeli